CLINICAL RESEARCH PROTOCOL

UNIVERSITY OF CALIFORNIA SAN DIEGO

DEPARTMENT OF MEDICINE

CLINICAL PROTOCOL NUMBER: RAMIC

TITLE: A Randomized, Double-blind**,** Placebo-Controlled Trial to Evaluate the Efficacy of Ramipril to Prevent ICU Admission, Mechanical Ventilation or Death in Persons with COVID-19

ABBREVIATED TITLE: RAMIC Trial

AMENDMENT: Amendment 6, December 9, 2020

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IDENTIFYING WORDS: SARS-CoV-2, hypertension, ACE inhibitor, Angiotensin II receptor blocker, mortality

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ESTIMATED DURATION OF STUDY: 1 year

NUMBER AND TYPE OF PATIENTS: Up to 560 patients with confirmed SARS-CoV-2 diagnosis, ages above 18 years, both male and female.

SUBJECTS OF STUDY:

Number of patients	Sex	Age Range
560	Male & Female	Above 18 years
Volunteers	None	

PROJECT USES IONIZING RADIATION: No

PROJECT USES "DURABLE POWER OF ATTORNEY": No

TYPE OF STUDY: Randomized-controlled-trial

MULTI-INSTITUTIONAL PROJECT: Yes

The RAMIC Trial

A Randomized, Double-blind**,** Placebo-Controlled Trial to Evaluate the Efficacy of Ramipril to Prevent ICU Admission, Mechanical Ventilation or Death in Persons with COVID-19

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with applicable United States (US) Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; Good Clinical Practice (GCP) guidelines; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

I agree to conduct the study according to all stipulations of the protocol, including all statements regarding confidentiality, and according to applicable legal regulations and regulatory requirements.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____

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ABSTRACT

As of early April, 2020, the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 1.1 million people globally and caused over 62,000 deaths. Currently, no drug therapies have yet been proven to be effective in treating COVID-19 patients, although several are under investigation or in development. Among COVID-19 cases, pre-existing comorbidities such as hypertension, diabetes, and cardiovascular disease have been shown to be associated with higher risk of developing severe symptoms and higher risk of mortality[1]. Recent data suggest that use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) may be associated with lower risk of morbidity and mortality in patients with COVID-19[2,3,4].

ACEIs and ARBs are part of the renin-angiotensin-aldosterone system (RAAS) inhibiting agents and considered as one of the first-line therapies for the management of a large proportion of patients with hypertension. However, continued use of ACEI/ARB has become controversial in the setting of COVID-19. The reason for this controversy stems from the fact that ACEIs and ARBs use may increase the expression of ACE2 receptor[5-7], which is the known cellular receptor and a necessary entry point for SARS-COV-2 infection[8]. Therefore, continued use of ACEIs and ARBs among patients with COVID-19 infection is controversial due to theoretical concerns of potentially increased cellular invasion of SARS-COV-2 or enhanced susceptibility towards SARS-COV-2 infection. Conversely, it has been indicated that ACE2 expression is downregulated following SARS infection, resulting in excessive activation of RAAS and exacerbated pneumonia progression mediated by angiotensin[9,10]. Therefore, administration of ACEI/ARB may in turn be beneficial by blocking the angiotensin-induced hyperactivation of RAAS and thereby preventing acute lung injury and risk of adult respiratory distress syndrome in patients with COVID-19.

Ramipril is an ACE inhibitor that is approved by the FDA for the treatment of hypertension, to reduce the risk of heart failure and death post-myocardial infarction, and reduction of risk of myocardial infarction, stroke, and death from cardiovascular causes. The drug's suppressing effects on the renin-angiotensin-aldosterone system (RAAS) system leads to inhibition of tissue and circulating ACE activity. This leads to cessation of angiotensin II-related vasoconstrictive, proinflammatory, and pro-oxidative effects and improvement in hypertension, inflammation and oxidative stress. These properties may be useful.

Ramipril has not been studied in SARS-CoV-2 infected patients. In this study we propose to treat 560 patients with ramipril or placebo for 14 days. After an initial evaluation for COVID-19 status, medical history, and symptom assessment, patients will receive either 2.5 mg/day of ramipril or placebo. Patients' symptoms and study endpoints will be monitored at regular intervals. Additional follow-up will be performed at day 28. As an exploratory objective, biomarkers of the RAAS axis will also be monitored. The primary endpoints of successful therapy will be improved survival, reductions in ICU admissions, and/or reductions in use of mechanical ventilator support. Secondary endpoints will be the proportion of patients needing continued hospitalization, time to mortality, time to ICU admission, time to discharge from hospital, proportion of patients developing hypotension and needing pressor support, and proportion of patients developing septic shock.

BACKGROUND

The global coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[11], is projected to infect millions of people worldwide and lead to 240,000 deaths in the United States. Currently, no drug therapies have been proven to be effective in treating COVID-19 patients, although several are under investigation or in development. Emerging data suggest hypertension, along with diabetes and cardiovascular disease, predisposes individuals to increased risk for more severe COVID-19 symptoms and higher mortality[1]. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) block the renin-angiotensin aldosterone system (RAAS) and are commonly prescribed treatments for patients with these conditions. Use of this drug class for COVID-19 patients has been a subject of controversy, because they have been reported in animal studies to increase expression of ACE2, the known receptor and cellular entry point for SARS-CoV-2, and thus may increase susceptibility to the virus[5,6]. Supporting this observation, higher urinary and circulating ACE2 levels have been observed in patients with hypertension and diabetes, respectively, who underwent treatment with ARBs and ACEIs[76].

Use of ACEIs/ARBs in COVID-19 patients: However, several lines of evidence suggest use of ACEIs and ARBS may offer protective effects in COVID-19 patients. A recent study from Shenzhen, China reported that serum angiotensin II levels were significantly elevated in COVID-19 patients with pneumonia and were linearly correlated with viral load and lung injury[2]. This observation, combined with animal studies, has led to the hypothesis that SARS-CoV-2 infection may lead to downregulation of ACE2 expression and subsequent activation of the RAAS system, which in turn may contribute to the severe levels of lung injury and respiratory failure widely observed in hospitalized COVID-19 patients[2,12]. If this working model is correct, use of ACEIs and ARBs may offer therapeutic benefit in treatment of the COVID-19 patient population. This hypothesis is supported by another recent study of 1128 adult COVID-19 patients admitted to 9 hospitals in Hubei Province, China[3]. In this retrospective cohort study of hospitalized COVID-19 patients with hypertension, the 28-day all-cause mortality rate among patients who had inpatient treatment with ACEI/ARB (n=188) compared with ACEI/ARB nonusers (n=940) was 3.7% vs 9.8%, a difference that was statistically significant. In this study, inpatient ACEI/ARB treatment associated with a lower mortality risk, although the findings may be influenced by confounding factors. Further support comes from previous studies showing ACEIs/ARBs may benefit patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)[13-16].

Ramipril: First approved for clinical use nearly 3 decades ago, Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative that has potent antihypertensive properties. It undergoes de-esterification in the liver to form ramiprilat, its active metabolite and a nonsulfhydryl ACE inhibitor. Ramipril is approved by the FDA for the treatment of hypertension, to reduce the risk of heart failure and death post-myocardial infarction, and reduction of risk of myocardial infarction, stroke, and death from cardiovascular causes. The drug's mitigating effects on hypertension are largely attributed to its suppression of the RAAS system. Ramipril's inhibition of tissue and circulating ACE activity results in reduced angiotensin II formation. The drug is generally well tolerated with the most prevalent adverse effects in patients with hypertension being headache, dizziness, and fatigue.

Hypothesis

We hypothesize that Ramipril 2.5 mg po once daily will perform better than placebo in reducing the composite of all-cause mortality, need for ICU admission or invasive mechanical ventilator support among hospitalized patients with COVID-19.

Specific Aims

We plan to conduct a randomized, double-blinded, placebo-controlled clinical trial to examine the efficacy of ramipril at 2.5 mg orally daily versus placebo given over 14 days to improve COVID-19 patient outcomes including mortality, ICU admission rates, and rates of invasive mechanical ventilator use.

In this study, we propose to randomize up to 510 patients with SARS-CoV-2 infection, as confirmed by PCR or clinical presentation consistent with COVID-19 infection (fever or cough or shortness of breath) with positive IgM serology, to either ramipril or placebo for 14 days. We plan to enroll a total of 560 patients, expecting some drop outs prior to randomization. After an initial medical history and screening labs and procedures, patients will be randomized to receive either ramipril 2.5 mg or placebo orally for 14 days. Patients' symptoms and study endpoints will be monitored at regular intervals. After 14 days, in patient participants will undergo end-of-treatment visit with collection of lab results from medical records, if done as part of routine medical care. An additional follow-up visit will be performed at day 28. For outpatient participants, the Day 14 and Day 28 visits will be virtual.

As an exploratory objective, biomarkers of the RAAS axis, will also be monitored in a subset of patients. The primary endpoints of successful therapy will be improved survival, reductions in ICU admissions, and/or reductions in use of invasive mechanical ventilator support. Secondary endpoints will be the proportion of patients needing continued hospitalization, time to mortality, time to ICU admission, time to discharge from hospital, proportion of patients developing hypotension and needing pressor support, acute kidney injury and proportion of patients developing septic shock.

STUDY OBJECTIVES AND OUTCOMES

Primary objective:

To examine the efficacy of ramipril 2.5 mg orally daily over 14 days versus placebo in patients with COVID-19 infection in improving survival and reduction in need for admission to intensive care unit or invasive mechanical ventilation.

Secondary objectives:

Proportion of patients needing continued hospitalization at day 14
Time to discharge from the hospital
(For discharged to outpatient sub-group only) Need for hospitalization
Proportion of patients developing hypotension and needing pressor support
Proportion of patients developing septic shock defined as sepsis with hypotension requiring vasopressors to maintain MAP ≥ 65 and serum lactate > 2 mmol/L after fluid resuscitation (Sepsis-3 JAMA 2016)
Acute kidney injury defined by KDIGO guidelines, increase in serum creatinine by ≥ 0.3 mg/dL within 24 hours or increase in serum creatinine ≥ 1.5 times baseline.
Composite of mortality or need for ICU admission or invasive mechanical ventilator use within a 28-day window

Exploratory objective:

To examine the efficacy of ramipril in improving biomarkers of the renin-angiotension-aldosterone axis

To examine racial differences in response to treatment with ramipril in patients with COVID-19 infection

Primary outcome measure:

Composite outcome includes mortality (yes/no) or need for ICU admission or invasive mechanical ventilation (yes/no) at 14-day from the start of treatment (or at any point within the 14-day window).

Secondary outcomes:

1. Proportion of patients needing continued hospitalization at day 14
2. Time to discharge from the hospital
3. (For outpatient sub-group only) Need for hospitalization
4. Proportion of patients developing hypotension and needing pressor support
5. Proportion of patients developing septic shock
6. Proportion of patients developing acute kidney injury
7. Composite of mortality or need for ICU admission or invasive mechanical ventilator use within a 28-day window

STUDY DESIGN

This is a randomized, double-blinded, placebo-controlled clinical trial to examine the efficacy of ramipril at 2.5 mg orally daily versus placebo given over 14 days to improve outcomes in patients with documented COVID-19 infection. 560 subjects will be randomized, monitored at regular intervals for the 14 days, and will be invited to continue participating in the study for an additional 1 year for monitoring. Study participants and investigators will be blinded to study assignment.

Randomization

Randomization will occur in a 2:1 ratio to treatment and placebo study arms respectively using permuted block randomization by UCSD investigational drug services.

Recruitment

Recruitment will occur through referral from patients presenting to the emergency department, urgent care, other ambulatory clinics or currently hospitalized. In addition, system lists generated to track patients undergoing testing for COVID-19 infection will be used for recruitment in accordance with the partial HIPAA waiver. Study sites will communicate study availability to their emergency departments, urgent care, other ambulatory clinics and hospital wards. Given the scope of the pandemic and lack of effective therapies we anticipate rapid study accrual.

Study Visits

All subjects: Study visits will occur virtually and in accordance with IRB guidelines to reduce the risk of SARS-CoV-2 transmission and preserve personal protective equipment. Informed consent will be obtained by study personnel by videoconference or telephone. A HIPAA waiver will be completed by study subjects so that study personnel can extract relevant data from the medical record. Subjects may be asked to provide copies of their COVID-19 test results, medical history, imaging results and concomitant medications. Subsequent study visits will occur by videoconference or telephone.

Inpatients only: Regular laboratory assessment will be extracted from the medical record on inpatients.

Discharged to outpatient only: A mobile phlebotomy unit maybe used for blood draws for outpatient subjects (Sites will seek approval from UCSD prior to use of third party vendor for mobile phlebotomy services). Patients discharged from the hospital at any point after randomization will receive sufficient drug/placebo to complete the study and will continue to be monitored by videoconference or telephone and will follow up for end of treatment (EOT)/Day 14.

SUBJECT SELECTION

Inclusion Criteria:

- Age ≥ 18 years
- Willing and able to provide written informed consent prior to performing study procedures OR legally authorized representative has been fully informed and has given voluntary written informed consent in compliance with local regulations.
- Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 7 days before randomization
  OR
  Clinical presentation consistent with COVID-19 infection (fever or cough or shortness of breath) with positive IgM serology

Exclusion Criteria:

- Participation in any other clinical trial of an experimental treatment for COVID-19 (compassionate use of hydroxycholoroquine, choloroquine, azithromycin or emergency use authorization of remdesivir outside of a clinical trial is allowed)
- Requiring mechanical ventilation at screening
- Requiring ICU care at admission/screening visit
- NSAID use within 12 hours of randomization or requiring continued NSAID use during this trial. Use of ASAs is permitted.
- Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN)
- Estimated GFR < 40 mL/min
- History of serum creatinine ≥ 2 mg/dl in the previous 28 days
- Systolic BP < 100 mm hg or diastolic BP < 65 mm hg
- Hypersensitivity to ACEI
- History of angioedema
- Outpatient use of ACE inhibitor or Angiotensin II receptor blocker in the last 7 days
- History of renal artery stenosis
- Serum potassium ≥ 5.1 mEq/L
- Pregnancy or breastfeeding
- Use of aliskiren, amifostine, lithium, sacubitril, within 7 days

Subject Enrollment:

Prior to initiating the study, each site must have the protocol and informed consent form approved as appropriate by the appropriate institutional review board or ethics committee. Potential subjects may be referred to the research team in one of two ways 1) Patients with positive PCR testing for SARS-COV2 or with positive IgM serologic testing for SARS-COV2 and clinical presentation consistent with infection

(fever or cough or shortness of breath) who present to the emergency department, urgent care, other ambulatory clinics or are hospitalized may be referred to participate. Patients with a clinical suspicion of COVID-19 infection may also be referred to participate. Candidates referred to the study will undergo informed consent using one of the following: 1) Subjects will be consented in-person, or by videoconference or telephonically, which must occur in the presence of a co-signing witness. A paper copy of the consent form can be provided by a designated health care provider caring for the patient. 2) Alternately, electronic methods may be used for consenting subjects. An electronic copy of the signed consent will be provided to the subject. After obtaining informed consent, a structured interview will be performed to review the past medical history and medication history. Requisite screening labs and procedures will be reviewed. Patients meeting all eligibility criteria and having no exclusion criteria will be enrolled in the study. The screening process is outlined in Appendix A (Screening Diagram).

TREATMENT

Subjects meeting all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment. The subject will be considered to be randomized when the first dose of investigational product is ingested. Participants will be randomized one of two treatment arms and receive either ramipril 2.5 mg/day (1 capsule) or placebo (1 capsule) orally for a total of 14 days. Study drug is supplied by Pfizer Inc. to the site pharmacist who will then distribute the appropriate drug/placebo to the inpatient pharmacy for distribution to the patient. Alternately, the site investigator may receive and dispense study drug to the subjects. The study site pharmacist/site investigator is required to maintain records of all study drug/placebo administration. Study drug/placebo should preferentially be administered after 8 hours of fasting.

At each visit, particular attention will be paid to symptoms associated with the possible side effects of ramipril and patients will complete a standardized symptom scale.

All patients will be advised to abstain from concomitant NSAID while on study drug/placebo. Use of ASAs are permitted during the trial.

Inpatients: For patients admitted to the hospital, a 14-day supply of study drug/placebo will be provided to the inpatient pharmacy from the site pharmacist for daily administration by the health care team. Participants were advised to consume the drug in the morning after eight hours of fasting.

Discharged to outpatient: For outpatient subjects, study drug/placebo will be provided to complete a 14-day treatment course. Participants were advised to consume the drug in the morning after eight hours of fasting.

STUDY ASSESSMENTS

Study subjects will attend a virtual information session during which the primary consent document, and the UCSD HIPAA forms are reviewed, discussed and signed. The following study procedures will be completed at this visit for all study subjects:

1. Review concomitant medication use
2. Review past medical history
3. Review and record blood tests. Complete blood count (CBC) and Comprehensive Metabolic Panel (CMP) are required and should be obtained through the study if not obtained for routine clinical care.
4. Review and record clinical chest x-ray and computed tomography results, if available.
5. Review vital signs: heart rate, blood pressure, oxygen saturation and the use of supplemental oxygen, body temperature, and respiratory rate, if available.
6. Symptom assessment: Structured tool (Appendix B)
7. Outcome assessment

Table 1: Schedule of Events

Assessment		Treatment Period				End of Study	Early Termination
Visit Date	Screening	RAND	D3	D7	D14	D28	
Visit Window						± 7	
Visit	V1	V2	V3	V4	V5	V6	ET
Informed Consent	X						
Review of Positive SARS-CoV-2 Molecular Test	X						
Screening Labs and Procedures[1]	X						
Medical History	X						
Concomitant Medication History	X	X[2]	X	X	X	X	X
Collect Vital Signs		X					
Imaging Data Extraction		X					
Biomarker Assessment and Biobank[3]	X[6]	X		X inpatient only	X inpatient only	X inpatient only includes serologic testing	
Symptom Assessment (Telephone or Video)		X	X	X	X	X	X

Laboratory Assessment[4]		X[5]	X inpatient only	X inpatient only	X inpatient only	X inpatient only	X inpatient only
Dispensing of Study Drug		X					
Review of Treatment Adherence			X	X	X	X	X
AE/SAE Assessment		X	X	X	X	X	X
Study Endpoint Determination			X	X	X	X	X

Boxes shaded red are required study procedures. Others are as available. All procedures apply to both inpatients and outpatients, unless otherwise indicated.

[1]As outlined in study figure: Complete blood count with differential, comprehensive metabolic panel, oxygen saturation and confirmation of pregnancy status. These tests should be obtained through the study if not obtained for routine clinical care.

[2]Only required if greater than 24 from screening visit

[4]Laboratory assessment: Complete blood count with differential, comprehensive metabolic panel.

Premature Discontinuation of Study Drug

Patients meeting a primary endpoint for the study defined as invasive mechanical ventilation or transfer to the intensive care unit or death will stop study drug/placebo. In addition, patients who discontinue due to toxicity rules defined below may stop the study drug/placebo. Additional data on secondary endpoints will continue to be collected and the SOE will be completed when possible.

Post-Treatment Phase:

At the end of the 14-day treatment phase, patients will be followed for another 14 days until day 28 and receive a phone visit to assess any changes in the clinical status related to primary and secondary outcomes. It is not possible to predict the outcome of this study, but if ramipril appears to have a significant effect on COVID-19 outcomes, we will likely develop a follow-up protocol to assess its impact on long-term virologic cure, immune function, lung function and long-term survival and re-infection due to COVID.

ADVERSE EVENTS AND STUDY MONITORING

Safety will be assessed on a continuous basis in the study. Adverse events are any unfavorable or unintended sign, symptoms or diagnosis that occurs in a study participant during the conduct of the study independent of attribution. All adverse events will be recorded on case report forms within 72 hours if it meets any of the following criteria: ≥ Grade 3 toxicity (per Table 2) or those that lead to cessation of study drug/placebo regardless of toxicity.

Risks and hazards of Ramipril:

First approved for clinical use nearly 30 years ago, ramipril has been evaluated for safety in over 4,000 patients with hypertension[17-21]. In placebo-controlled trials, the most frequent clinical side effects reported included headache (5.4%), dizziness (2.2%), and fatigue (2.0%). Only fatigue has been observed to be more common in ramipril groups, compared to the placebo group. Side effects have generally been observed to be mild and transient and were not dose-dependent. Discontinuation of ramipril due to side effects occurred in 3% of US patients in clinical trials. The common reasons cited for discontinuation were: cough (1.0%), dizziness (0.5%), and impotence (0.4%). In the Heart Outcomes Prevention Evaluation study (HOPE study)[22-23], 4,645 patients taking ramipril 10 mg daily were followed over a 5-year period. Patients in this study were either normotensive or under treatment with other antihypertensive agents. In this study, the only notable side effect that led to excess discontinuation of ramipril was cough. Ramipril is a well-studied and reasonably safe drug. However, we will monitor study subjects carefully for any adverse reactions either via physical exams for inpatients or through remotely conducted visits by phone or video for outpatients.

Criteria for discontinuation

Any patient meeting ≥ Grade 3 toxicity (per Table 2) or meeting the primary endpoint will have the study drug/placebo discontinued. There is no recommended dose modification. Outpatients will also be screened for symptoms and those with symptoms consistent with any of the below adverse events will be assessed by the site PI to determine the need for cessation of study drug/placebo.

Table 2. Scoring of toxicity for discontinuation

Adverse events	1	2	3	4	5
Allergic reaction	Transient flushing or rash, Intervention not indicated	Intervention or infusion interruption indicated; Responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); Prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); Recurrence of symptoms following initial improvement; Hospitalization indicated for clinical sequelae (e.g., renal impairment,	Life threatening consequences; Urgent intervention indicated	Death

			pulmonary infiltrates)		
Anaphylaxis			Symptomatic bronchospasm, with or without urticaria; Parenteral intervention indicated; Allergy-related edema/angioedema; Hypotension	Life-threatening consequences; Urgent intervention indicated	Death
Hypotension			SBP < 90 mm hg or DBP < 50 mm hg	Requiring vasopressor support	Death
ALT (U/L)	Baseline-1.5x baseline	>200 and > 1.5x baseline	>400 and > 2x baseline	401-800 and > 3x baseline	>800
AST (U/L)	Baseline-1.5x baseline	>200 and > 1.5x baseline	>400 and > 2x baseline	401-800 and > 3x baseline	>800
Total Bilirubin (mg/dL)	0.1 to 1	1.1 to 2 and direct bilirubin >0.5	2 to 5 and direct bilirubin > 1	5.1 to 10	>10
Potassium (mg/dL)	5.1-5.3	> 5.3-5.5	> 5.5- 6.0 Investigator can assess for possible hemolysis	> 6.0	Death
Creatinine (mg/dL)	Creatinine level increase of >0.3 mg/dL; Creatinine 1- 1.5 x above baseline	Creatinine 1.5 - 2x above baseline	Creatinine >2x baseline or >2.0 mg/dL; Hospitalization indicated	Life-threatening consequences; Dialysis indicated	Death

Table 2. Scoring of toxicity for dose modification. Scoring of toxicity from the CTC Version 4.0, with modifications is proposed given the short duration of therapy and consideration of signs and symptoms

related to COVID-19 infection. Due to the nature of the trial and to minimize exposure to SARS-CoV2 monitoring laboratory assessments while on study drug/placebo will only occur in hospitalized patients. Grade 3, 4, 5 reactions warrant drug/placebo discontinuation

The risks and discomforts of frequent phlebotomy

Blood samples will be obtained to document changes in levels of biochemical markers of the RAAS system and to monitor the metabolic effects and toxicities of ramipril. Blood collection by venipuncture is associated with mild discomfort, and the possibility of localized bruising, phlebitis, or extravasation. The risk of infection or fainting is extremely small.

Data and Safety Monitoring

The UC San Diego Clinical and Translational Research Institute will appoint an independent data safety monitoring board (DSMB) composed of two independent physicians and one statistician. The DSMB will undertake a review of the interim data from the study to ensure the safety of study participants and to recommend changes to the study including early termination or modification of the study if it appears futile. The DSMB will review a summary of data by randomized treatment arm for the primary outcome, toxicity and adverse events. A planned interim analysis will occur after approximately 50% of the planned enrollment from the trial has been completed, approximately 280 patients.

The principal investigator and research coordinator of this protocol will monitor data and safety regularly at weekly meetings. These meetings are separate from regular clinical rounds and consist of review of all study patients including flow sheets of major safety and efficacy measurements. All measurements and tests are well established in clinical medicine. Yearly reports are made to the UCSD IRB regarding safety and efficacy.

Adverse Event Reporting

All serious adverse events will be reported to the local IRB and sponsor within 7 days. Unexpected and related fatal or life-threatening events will be reported within 48 hours and reports will be sent to the FDA, MEDWATCH program (telephone 1-800-FDA-1088; or via the Internet at www.fda.gov/medwatch/index.html.)

Patient Privacy

All data and study forms will be in secured locations (locked room or cabinet) and access is limited to study personnel. Subject names are not used; instead a name code is assigned upon enrollment. Release of data to persons or organizations outside study personnel will require written consent of the subject.

All consents will be stored in well-marked binders in locked file cabinets located in private offices at UCSD Medical center. Databases with identifying information will be secure as they will be password protected and encrypted. Staff will be trained in HIPPA guidelines and confidentiality issues.

STATISTICAL METHODS AND CONSIDERATIONS

The primary outcome of this study will be represented by a composite of outcomes which will include mortality, ICU admission, and/or need for ventilator use within a 14-day period. Statistical analyses will compare outcomes between treatment versus placebo-arms. It is not possible to predict what the spontaneous or therapeutic response rate will be. Thus, we predict that the spontaneous improvement rate would be zero to less than 1%. In the primary analysis, we assume that the 14 day mortality/ICU admission/Ventilator use of placebo and ramipril-treatment group to be 22% and 12%, and the proportion of the sample from placebo to ramipril-treatment group to be 1:2. Therefore, using Whittemore's formula (Whittemore, 1981), we estimate a sample size of 510 patients--340 in the ramipril arm and 170 in the placebo arm—will be required to detect effects with a power 80% (or higher) with a Type I error rate of alpha = 0.05. This formula is used for logistic regression which has an overall event proportion of P and an odd ratio of r at one standard deviation above the mean of the predictor.

Statistical analysis plan:

The primary outcome will first be analyzed using a 2x2 contingency table (treatment by outcome) and testing will use Fisher's exact test. Primary analyses will be Intent to Treat (ITT).

We expect to enroll up to 560 patients in this study and randomize at least 510 of them to either treatment or placebo arm for a full 2 weeks with a follow-up evaluation. Therapeutic intervention trials have had variable dropout rates. Previous short-term studies of ramipril had less than 10 % dropouts. Therefore, we expect less than a 10% dropout rate. Dropouts would be considered non-responders based upon intention to treat analysis. A modified intention to treat analysis will be done in which we will exclude the patients who dropped out before getting the week 2 exit evaluation.

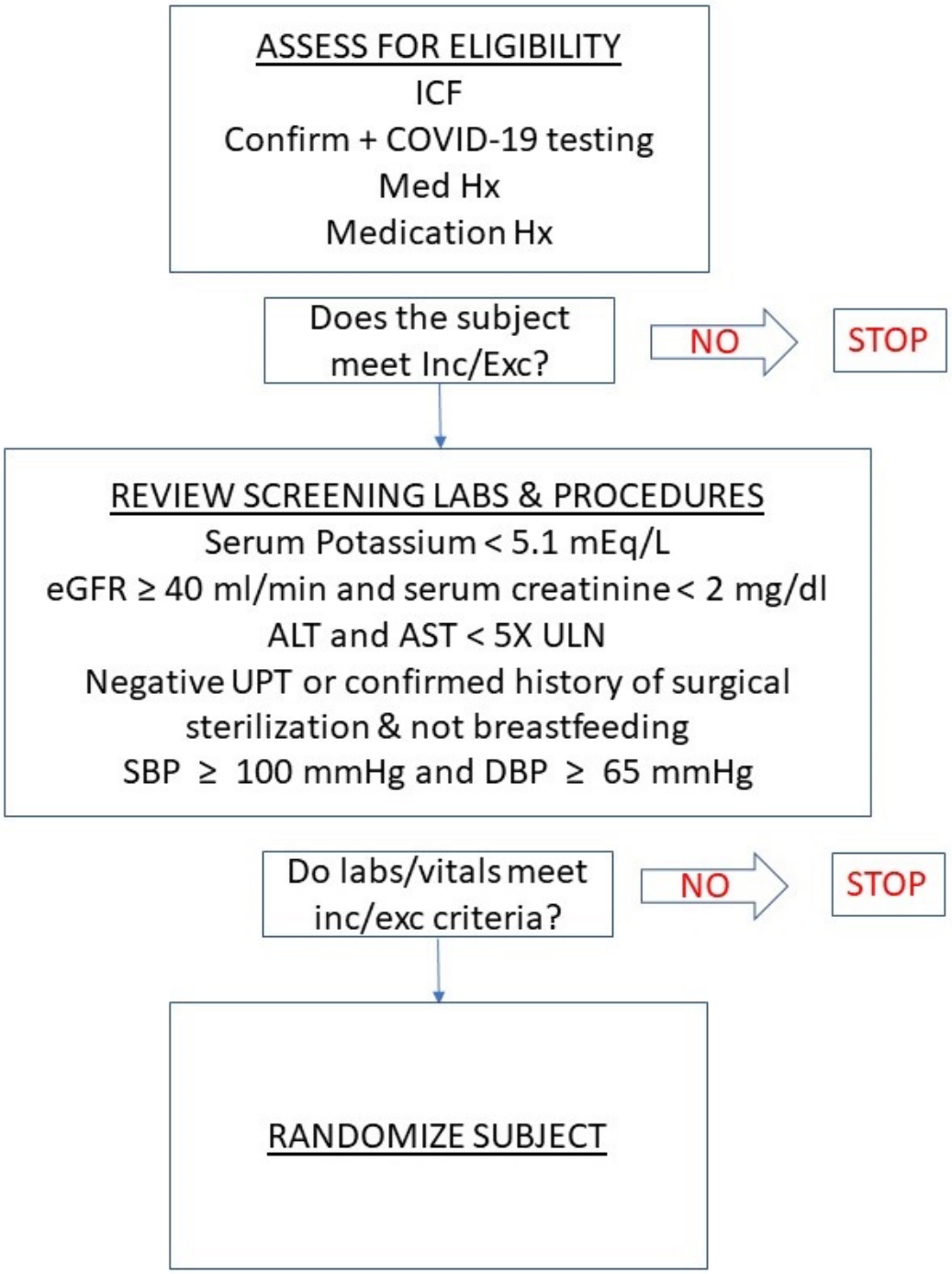
Primary and secondary outcomes will be assessed comparing placebo and treatment arms using parametric or non-parametric tests as indicated.

The major **primary outcome** to be evaluated is a composite of mortality or need for ICU admission or invasive mechanical ventilator use within a 14-day window.

The major **secondary outcomes** to be evaluated are:

1. Proportion of patients needing continued hospitalization at day 14
2. Time to discharge
3. (For discharged to outpatient sub-group only) Need for hospitalization
4. Proportion of patients developing hypotension and needing pressor support
5. Proportion of patients developing septic shock
6. Proportion of patients developing acute kidney injury
7. Composite of mortality or need for ICU admission or invasive mechanical ventilator use within a 28-day window

APPENDIX A: Screening Diagram



APPENDIX B: COVID-19 Symptom Assessment

COVID-19 Symptom Assessment

Pt ID_____

Purpose: To evaluate the symptoms of COVID-19 infection

1. Has the patient had a fever?

Never	Yes
(0)	(1)

→ Proceed to question 3

2. What was the highest measured temperature in the last 24 hours?
   _____ Farenheit

3. Is the patient short of breath or trouble breathing?

No	Yes
(0)	(1)

4. Does the patient have a cough?

No	Yes
(0)	(1)

5. Does the patient have loss of sense of smell or change in taste?

No	Yes
(0)	(1)

6. Does the patient have light-headedness?

No	Yes
(0)	(1) → Alert site investigator to follow up

7. Does the patient have body aches?

No	Yes
(0)	(1)

8. Does the patient have chest pain?

No	Yes
(0)	(1)

9. Does the patient have drenching sweats?

No	Yes
(0)	(1)

10. Does the patient have diarrhea?

No	Yes
(0)	(1)

Completed by _____

Signature _____

Date _____

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